



PATENT
Attorney Docket No. 207596
DHHS Ref: E-200-98/3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Erickson et al.

Application No. 09/720,276

Filed: March 7, 2001

For: FITNESS ASSAY AND ASSOCIATED METHODS

Group Art Unit: 1648

Examiner: S. A. Foley

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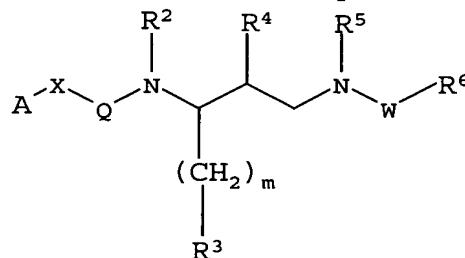
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**AMENDMENTS MADE TO CLAIMS
IN RESPONSE TO OFFICE ACTION OF OCTOBER 2, 2002**

(Deletions are indicated by bracketed text, while insertions are indicated by underlined text)

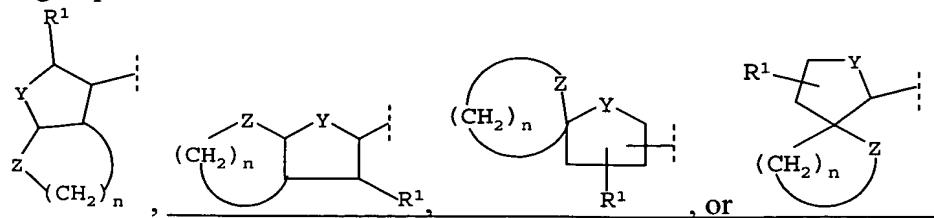
47. (Amended) A method of preventing the development of drug resistance in an HIV-infected mammal, said method comprising administering to said HIV-infected mammal a drug resistance-inhibiting effective amount of a compound of the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, or a pharmaceutically acceptable composition of said compound, said salt, said prodrug, or said ester thereof, wherein:

A is a group of the formula:



R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl, in which at least one hydrogen atom is optionally substituted with a substituent selected from the group

consisting of OR^7 , SR^7 , CN , NO_2 , N_3 , and a halogen, wherein R^7 is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Y and Z are the same or different and [are independently] each is selected from the group consisting of CH_2 , O, S, SO, SO_2 , NR^8 , $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are each selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10} , $CHR^{10}CH_2$, CH_2CHR^{10} , O, NR^{10} , or S, wherein R^{10} is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Q is $C(O)$, $C(S)$, or SO_2 ;

R^2 is H, a C_1 - C_6 alkyl, a C_2 - C_6 alkenyl, or a C_2 - C_6 alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of alkyl, $(CH_2)_pR^{11}$, OR^{12} , SR^{12} , CN , N_3 , NO_2 , $NR^{12}R^{13}$, $C(O)R^{12}$, $C(S)R^{12}$, CO_2R^{12} , $C(O)SR^{12}$, $C(O)NR^{12}R^{13}$, $C(S)NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}C(S)R^{13}$, $NR^{12}CO_2R^{13}$, $NR^{12}C(O)SR^{13}$, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3 , NH_2 , NO_2 , SH, and CN; and

R^{12} and R^{13} are the same or different and each is selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

R^4 is OH, =O (keto) or NH_2 , wherein, when R^4 is OH, it is optionally in the form of a pharmaceutically acceptable ester or prodrug, and when R^4 is NH_2 , it is optionally an amide, a hydroxylamino, a carbamate, a urea, an alkylamino, a dialkylamino, a protic salt thereof, or a tetraalkylammonium salt thereof;

R^5 is H, a C_1 - C_6 alkyl radical, a C_2 - C_6 alkenyl radical, or $(CH_2)_qR^{14}$, wherein q is an integer from 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3 , NH_2 , NO_2 , SH, and CN;

W is $C(O)$, $C(S)$, or SO_2 ; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting

of a halogen, OR^{15} , SR^{15} , $S(O)R^{15}$, SO_2R^{15} , $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN , $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3 , NO_2 , $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15} , $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, $P(O)(OR^{15})(OR^{16})$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylarnino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylarnino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an (arylarnino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylarnino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

wherein R^{15} , R^{16} , and R^{17} are the same or different and each is H, an unsubstituted alkyl, or an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is substituted with a substituent other than a halogen, OR^{15} , SR^{15} , CN , N_3 , NO_2 , $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15} , $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$, at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15} , SR^{15} , CN , N_3 , NO_2 , $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15} , $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$; and

wherein a mutant virus that is capable of evolving from the HIV virus infecting said mammal has lower fitness, relative to said HIV virus infecting said mammal, in the presence of said compound.

64. (Amended) The method of claim [62 or] 63, wherein said mutant retrovirus is a multidrug-resistant mutant retrovirus.

65. (Amended) The method of claim [62 or] 63, wherein said mutant retrovirus is a multidrug-resistant HIV [retrovirus].

66. (Amended) The method of claim [62 or] 63, wherein said mutant retrovirus is a multidrug-resistant HIV-1 [retrovirus].



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For: **FITNESS ASSAY AND ASSOCIATED METHODS**

PENDING CLAIMS AFTER AMENDMENT

1. An assay for determining the biochemical fitness of a biochemical target of a mutant replicating biological entity relative to its predecessor, comprising:

obtaining said predecessor,

determining the biochemical vitality of said biochemical target of said predecessor in the presence of a compound capable of inhibiting said biochemical target of said predecessor,

determining the biochemical vitality of said biochemical target of said mutant replicating biological entity in the presence of said compound, and

comparing the biochemical vitality of said biochemical target of said mutant replicating biological entity relative to the biochemical vitality of said biochemical target of said predecessor.

2. The assay of claim 1, wherein said predecessor is an infectious microorganism.

3. The assay of claim 2, wherein said infectious microorganism is a virus.

4. The assay of claim 3, wherein said virus is a retrovirus.

5. The assay of claim 4, wherein said retrovirus is HIV-1 or HIV-2.

6. The assay of claim 2, wherein said infectious microorganism is a malarial parasite.

7. The assay of claim 6, wherein said malarial parasite is a plasmodium species.

8. The assay of claim 2, wherein said infectious microorganism is a bacterium.
9. The assay of claim 1, wherein said predecessor is a cancer cell.
10. The assay of claim 9, wherein said cancer cell is a rapidly growing tumor cell.
11. The assay of claim 1, wherein said biochemical target of said predecessor is an enzyme and said compound inhibits said enzyme of said predecessor.
12. The assay of claim 1, wherein said biochemical target of said predecessor is a viral protease, a viral reverse transcriptase, a viral polymerase, a viral enzyme, or a viral protein.
13. The assay of claim 1, wherein said biochemical target of said malarial parasite is a plasmepsin, a plasmodial enzyme, or a protein.
14. The assay of claim 1, wherein said biochemical target of said predecessor is an oligomer and said compound inhibits the oligomerization of said oligomer of said predecessor.
15. The assay of claim 1, wherein said biochemical target of said predecessor is a protein and said compound inhibits a conformational change, ligand binding, or enzyme activity in said protein of said predecessor.
16. The assay of claim 11, wherein:
the biochemical vitality of the enzyme of said mutant replicating biological entity corresponds to $K_{inh\text{-}mut}$, $k_{cat\text{-}mut}$, and $K_M\text{-}mut$, and said biochemical vitality of the enzyme of said mutant replicating biological entity is defined by the relationship $K_{inh\text{-}mut}(k_{cat\text{-}mut}/K_M\text{-}mut)$, and
the biochemical vitality of the enzyme of said predecessor corresponds to $K_{inh\text{-}pred}$, $k_{cat\text{-}pred}$, and $K_M\text{-}pred$, and said biochemical vitality of the enzyme of said predecessor is defined by the relationship $K_{inh\text{-}pred}(k_{cat\text{-}pred}/K_M\text{-}pred)$,
wherein K_{inh} is an inhibition constant of said compound, k_{cat} is the biochemical catalytic rate, and K_M is the Michaelis constant.

17. The assay of claim 16, wherein $K_{inh\text{-mut}}$, $K_{inh\text{-pred}}$, $k_{cat\text{-mut}}$, $k_{cat\text{-pred}}$, $K_{M\text{-mut}}$, and $K_{M\text{-pred}}$ are each measured.

18. The assay of claim 16, wherein K_{inh} is K_j .

19. The assay of claim 16, wherein K_{inh} is K_d .

20. A method of administering a therapeutic compound that inhibits a biochemical target of a disease-causing replicating biological entity, comprising:

identifying at least one mutant capable of evolving from said disease-causing replicating biological entity,

determining a first biochemical vitality of said biochemical target of said disease-causing replicating biological entity in the presence of a first compound capable of inhibiting said biochemical target of said disease-causing replicating biological entity,

determining a first biochemical vitality of said biochemical target of said mutant replicating biological entity in the presence of said first compound,

determining a second biochemical vitality of said biochemical target of said disease-causing replicating biological entity in the presence of at least one additional compound capable of inhibiting said biochemical target of said disease-causing replicating biological entity,

determining a second biochemical vitality of said biochemical target of said mutant in the presence of said of at least one additional compound,

determining a first biochemical fitness of said biochemical target of said mutant relative to said disease-causing replicating biological entity by comparing the first biochemical vitality of said biochemical target of said mutant with the first biochemical vitality of said biochemical target of said disease-causing replicating biological entity,

determining a second biochemical fitness of said biochemical target of said mutant relative to said disease-causing replicating biological entity by comparing the second biochemical vitality of said biochemical target of said mutant with the second biochemical vitality of said biochemical target of said disease-causing replicating biological entity,

comparing the first biochemical fitness in the presence of said first compound with the second biochemical fitness in the presence of said at least one additional compound, and

administering, from among said first and said at least one additional compounds, a therapeutic compound which produces the lowest value for said first or said second biochemical fitness,
wherein said disease-causing replicating biological entity is less likely to develop resistance in the presence of said therapeutic compound.

21. The method of claim 20, wherein said replicating disease-causing replicating biological entity is an infectious microorganism.
22. The method of claim 21, wherein said infectious microorganism is a virus.
23. The method of claim 22, wherein said virus is a retrovirus.
24. The method of claim 23, wherein said retrovirus is HIV-1 or HIV-2.
25. The method of claim 21, wherein said infectious microorganism is a malarial parasite.
26. The method of claim 25, wherein said malarial parasite is a plasmodium species.
27. The method of claim 21, wherein said infectious microorganism is a bacterium.
28. The method of claim 20, wherein said disease-causing replicating biological entity is a cancer cell.
29. The method of claim 28, wherein said cancer cell is a rapidly growing tumor cell.
30. The method of claim 20, wherein said biochemical target of said disease-causing replicating biological entity is an enzyme and said compound inhibits said enzyme of said disease-causing replicating biological entity.

31. The method of claim 22, wherein said biochemical target of said disease-causing replicating biological entity is a viral protease, a viral reverse transcriptase, a viral polymerase, a viral enzyme, or a viral protein.

32. The method of claim 25, wherein said biochemical target of said malarial parasite is a plasmeprin, a plasmodial enzyme, or a protein.

33. The method of claim 20, wherein said biochemical target of said disease-causing replicating biological entity is an oligomer and said compound inhibits the oligomerization of said oligomer of said disease-causing replicating biological entity.

34. The method of claim 20, wherein said biochemical target of said disease-causing replicating biological entity is a protein and said compound inhibits a conformational change, ligand binding, or enzyme activity in said protein of said disease-causing replicating biological entity.

35. The method of claim 30, wherein:

the biochemical vitality of the enzyme of said mutant corresponds to $K_{inh\text{-}mut}$, $k_{cat\text{-}mut}$, and $K_{M\text{-}mut}$, and said biochemical vitality of the enzyme of said mutant is defined by the relationship $K_{inh\text{-}mut}(k_{cat\text{-}mut}/K_{M\text{-}mut})$, and

the biochemical vitality of the enzyme of said disease-causing replicating biological entity corresponds to $K_{inh\text{-}pred}$, $k_{cat\text{-}pred}$, and $K_{M\text{-}pred}$, and said biochemical vitality of the enzyme of said disease-causing replicating biological entity is defined by the relationship $K_{inh\text{-}pred}(k_{cat\text{-}pred}/K_{M\text{-}pred})$,

wherein K_{inh} is an inhibition constant of said compound, k_{cat} is the biochemical catalytic rate, and K_M is the Michaelis constant.

36. The method of claim 35, wherein $K_{inh\text{-}mut}$, $K_{inh\text{-}pred}$, $k_{cat\text{-}mut}$, $k_{cat\text{-}pred}$, $K_{M\text{-}mut}$, and $K_{M\text{-}pred}$ are each measured.

37. The method of claim 35, wherein K_{inh} is K_i .

38. The method of claim 35, wherein K_{inh} is K_d .

39. The assay of claim 1, wherein said predecessor is a wild-type HIV strain and said mutant has at least one mutation in the biochemical target thereof.

40. The method of claim 20, wherein said disease-causing replicating biological entity is a wild-type HIV strain and said mutant has at least one mutation in the biochemical target thereof.

41. The assay of claim 1, wherein said predecessor has at least one mutation in the biochemical target thereof, and said mutant has at least two mutations in the biochemical target thereof.

42. The method of claim 20, wherein said disease-causing replicating biological entity has at least one mutation in the biochemical target thereof, and said mutant has at least two mutations in the biochemical target thereof.

43. The method of claim 39, wherein said mutant has at least one active site mutation.

44. The method of claim 41, wherein said predecessor or said mutant has at least one active site mutation.

45. The method of claim 42, wherein said disease-causing replicating biological entity or said mutant has at least one active site mutation.

46. A continuous fluorogenic assay for measuring the anti-HIV protease activity of a protease inhibitor, which method comprises:

adding a solution of HIV protease to at least a portion of a substrate stock solution, in which the substrate has the formula Ala-Arg-Val-Tyr-Phe(NO₂)-Glu-Ala-Nle-NH₂, to provide a substrate reaction solution;

measuring the fluorescence of said substrate reaction solution at specified time intervals;

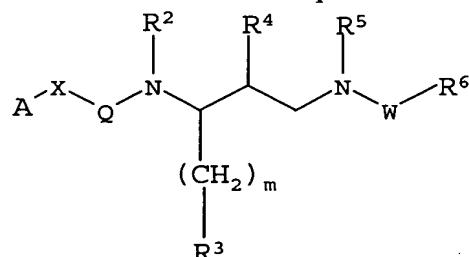
adding said solution of HIV protease to an inhibitor-substrate solution comprising a protease inhibitor and said substrate stock solution, to provide an inhibitor-substrate reaction solution;

measuring the fluorescence of said inhibitor-substrate reaction solution at specified time intervals; and

calculating the initial velocity of said inhibitor-substrate reaction solution by applying the equation:

$V=V_0/2E_t(\{[K_i(1+S/K_m)+I_t-E_t]^2+4K_i(1+S/K_m)E_t\}^{1/2}-[K_i((1+S/K_m)+I_t-E_t)])$, wherein V is the initial velocity of said inhibitor reaction solution, V_0 is the initial velocity of said substrate reaction solution, K_m is the Michaelis-Menten constant, S is the concentration of said substrate, E_t is the concentration of said protease, and I_t is the concentration of said inhibitor, wherein the initial velocities indicates the anti-HIV protease activity of said protease inhibitor.

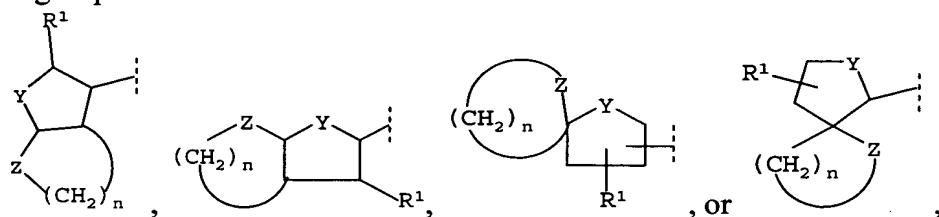
47. A method of preventing the development of drug resistance in an HIV-infected mammal, said method comprising administering to said HIV-infected mammal a drug resistance-inhibiting effective amount of a compound of the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, or a pharmaceutically acceptable composition of said compound, said salt, said prodrug, or said ester thereof, wherein:

A is a group of the formula:



R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl, in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of OR^7 , SR^7 , CN , NO_2 , N_3 , and a halogen, wherein R^7 is H , an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Y and Z are the same or different and [are independently] each is selected from the group consisting of CH_2 , O , S , SO , SO_2 , NR^8 , $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are each selected from the group consisting of H , an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10} , $\text{CHR}^{10}\text{CH}_2$, $\text{CH}_2\text{CHR}^{10}$, O, NR^{10} , or S, wherein R^{10} is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Q is C(O), C(S), or SO_2 ;

R^2 is H, a C₁-C₆ alkyl, a C₂-C₆ alkenyl, or a C₂-C₆ alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of alkyl, $(\text{CH}_2)_p\text{R}^{11}$, OR¹², SR¹², CN, N₃, NO₂, NR¹²R¹³, C(O)R¹², C(S)R¹², CO₂R¹², C(O)SR¹², C(O)NR¹²R¹³, C(S)NR¹²R¹³, NR¹²C(O)R¹³, NR¹²C(S)R¹³, NR¹²CO₂R¹³, NR¹²C(O)SR¹³, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH₃, NH₂, NO₂, SH, and CN; and

R^{12} and R^{13} are the same or different and each is selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

R^4 is OH, =O (keto) or NH₂, wherein, when R^4 is OH, it is optionally in the form of a pharmaceutically acceptable ester or prodrug, and when R^4 is NH₂, it is optionally an amide, a hydroxylamino, a carbamate, a urea, an alkylamino, a dialkylamino, a protic salt thereof, or a tetraalkylammonium salt thereof;

R^5 is H, a C₁-C₆ alkyl radical, a C₂-C₆ alkenyl radical, or $(\text{CH}_2)_q\text{R}^{14}$, wherein q is an integer from 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH₃, NH₂, NO₂, SH, and CN;

W is C(O), C(S), or SO_2 ; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OR¹⁵, SR¹⁵, S(O)R¹⁵, SO₂R¹⁵, SO₂NR¹⁵R¹⁶, SO₂N(OH)R¹⁵, CN, CR¹⁵=NR¹⁶, CR¹⁵=N(OR¹⁶), N₃, NO₂, NR¹⁵R¹⁶, N(OH)R¹⁵, C(O)R¹⁵, C(S)R¹⁵, CO₂R¹⁵, C(O)SR¹⁵, C(O)NR¹⁵R¹⁶, C(S)NR¹⁵R¹⁶, C(O)N(OH)R¹⁵, C(S)N(OH)R¹⁵, NR¹⁵C(O)R¹⁶, NR¹⁵C(S)R¹⁶, N(OH)C(O)R¹⁵, N(OH)C(S)R¹⁵, NR¹⁵CO₂R¹⁶, N(OH)CO₂R¹⁵, NR¹⁵C(O)SR¹⁶, NR¹⁵C(O)NR¹⁶R¹⁷, NR¹⁵C(S)NR¹⁶R¹⁷, N(OH)C(O)NR¹⁵R¹⁶, N(OH)C(S)NR¹⁵R¹⁶, NR¹⁵C(O)N(OH)R¹⁶, NR¹⁵C(S)N(OH)R¹⁶, NR¹⁵SO₂R¹⁶, NHSO₂NR¹⁵R¹⁶, NR¹⁵SO₂NHR¹⁶, P(O)(OR¹⁵)(OR¹⁶), an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a

cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (aryl amino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (aryl amino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an (aryl amino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroaryl amino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

wherein R^{15} , R^{16} , and R^{17} are the same or different and each is H, an unsubstituted alkyl, or an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is substituted with a substituent other than a halogen, OR^{15} , SR^{15} , CN , N_3 , NO_2 , $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15} , $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$, at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15} , SR^{15} , CN , N_3 , NO_2 , $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15} , $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$; and

wherein a mutant virus that is capable of evolving from the HIV virus infecting said mammal has lower fitness, relative to said HIV virus infecting said mammal, in the presence of said compound.

49. The method of claim 47, wherein:

when R^1 is an alkyl, it is a C_1 - C_6 alkyl;

when R^1 is an alkenyl it is a C_2 - C_6 alkenyl;

when R^1 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^1 is a 4-7 membered ring;

when R^7 , R^8 or R^9 is an unsubstituted alkyl, it is a C_1 - C_6 unsubstituted alkyl;

when R^7 , R^8 or R^9 is an unsubstituted alkenyl, it is a C_2 - C_6 unsubstituted alkenyl;

R^3 is a 4-7 membered ring;

R^{11} is a 4-7 membered ring;

when R^{12} or R^{13} is an unsubstituted alkyl, it is a C_1 - C_6 unsubstituted alkyl;

when R^{12} or R^{13} is an unsubstituted alkenyl, it is a C_2 - C_6 unsubstituted alkenyl;

when R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^{14} is a 4-7 membered ring;

when R^6 is a cycloalkyl, a heterocycloalkyl, aryl, or a heteroaryl, R^6 is a 4-7 membered ring;

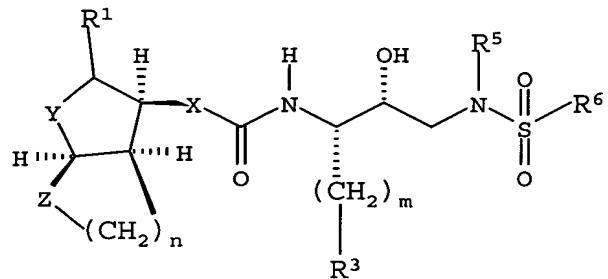
when R⁶ is substituted with a substituent that is an alkyl, an alkylthio, or an alkylamino, the substituent comprises from one to six carbon atoms; and

when R⁶ is substituted with a substituent that is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, the substituent is a 4-7 membered ring;

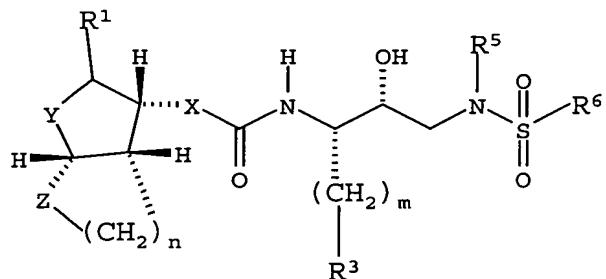
or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

50. The method of claim 47, wherein Q is C(O), R² is H, and W is SO₂, or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

51. The method of claim 47, wherein said compound is represented by the formula:

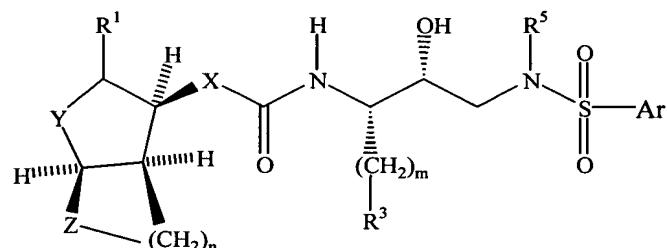


(IA) or

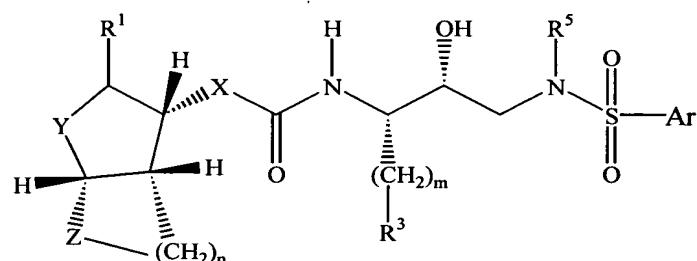


(IB).

52. The method of claim 51, wherein said compound is represented by the formula:



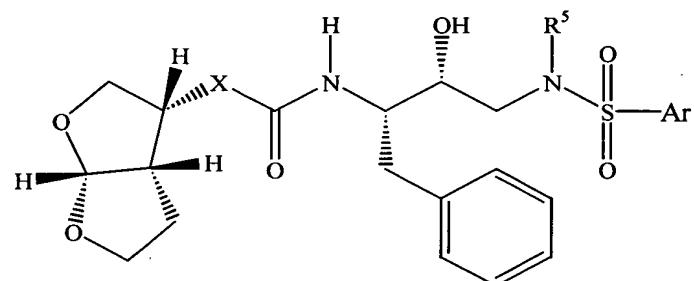
(IC) or



(ID),

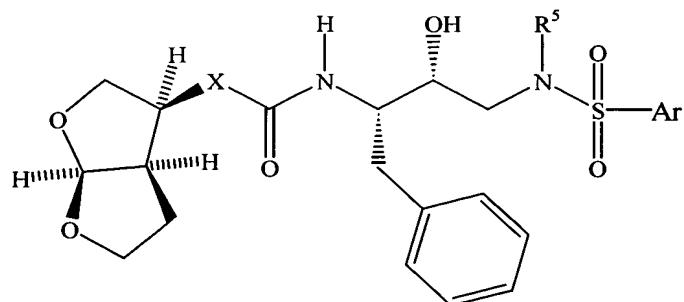
wherein Ar is a phenyl which is optionally substituted with a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl.

53. The method of claim 52, wherein said compound is represented by the formula:



(IE)

or



(IF).

54. The method of claim 52, wherein X is oxygen.
55. The method of claim 52, wherein R⁵ is isobutyl.
56. The method of claim 52, wherein Ar is a phenyl substituted at the para-position.
57. The method of claim 52, wherein Ar is a phenyl substituted at the meta-position.
58. The method of claim 52, wherein Ar is a phenyl substituted at the ortho-position.
59. The method of claim 52, wherein Ar is selected from the group consisting of para-aminophenyl, para-tolyl, para-methoxyphenyl, meta-methoxyphenyl, and meta-hydroxymethylphenyl.
60. The method of claim 47, wherein said HIV-infected mammal is infected with a wild-type HIV.
61. The method of claim 47, wherein said HIV-infected mammal is infected by a mutant HIV with least one protease mutation.
62. The method of claim 47, wherein said HIV-infected mammal is infected by a mutant HIV having at least one reverse transcriptase mutation.

63. A method of treating a mutant retroviral infection in a mammal infected with a mutant retrovirus, which method comprises administering to said mammal a mutant retroviral-inhibiting effective amount of a compound or composition defined in claim 47.

64. The method of claim 63, wherein said mutant retrovirus is a multidrug-resistant mutant retrovirus.

65. The method of claim 63, wherein said mutant retrovirus is a multidrug-resistant HIV.

66. The method of claim 63, wherein said mutant retrovirus is a multidrug-resistant HIV-1.